Type of Leukemia	**Incidence per 100,000***
Overall	6–10
CML	1–2
CLL	2–3
AML	2–3
ALL	3–4 (25% children)

Role of radiotherapy in leukemia:

1. **CNS Prophylaxis *(pre-symptomatic CNS therapy)***
2. **Treatment for extra-medullary relapse.**
3. **TBI in BMT conditioning**
   - *** ALL in 2nd CR**
   - *** ALL in high risk group in 1st CR**
   - *** CML**
   - *** AML in 1st CR (allo-BMT—56% EFS)**

50% long survivors

4. **palliative**

Risk adapted treatment is a new approach allows children who have a very good outcome with modest therapy to be spared more intensive & toxic treatment , while allowing children with a historically lower probability of long-term survival to receive more intensive therapy that may increase their chance of cure.

- **Risk classification is based in part, on *clinical features*, the most important of which are age & leukocyte count at time of diagnosis.**
- **An NCI workshop (USA) defined the Standard-risk group as consisting of children aged 1-9 years with an initial WBC count of less than 50,000/mm3; all other patients considered to have High-risk ALL.**
- **Standard-risk group had 80% 4-year estimated EFS.**
- **High-risk group had 60 % 4-year estimated EFS**

LOW RISK

B-cell precursor phenotype & age 1-9 Yr with TLC <50 000

Without CNS or testicular leukemia, a good early response to Treatment

STANDARD RISK

T- cell phenotype & B- cell precursor cases not classified As low or high risk

HIGH RISK

T(9;22) or BCR-ABL fusion with TLC > 50, 000 or poorly early response; Infants , or induction failure or > 5% blasts On day 22 of induction treatment or with extramedullary (CNS-testicular) disease

SUCCESSFUL TREAMENT = Control of Systemic disease (clear bone marrow, liver, spleen, Lymph nodes from blasts). "Treatment or Prevention Of extramedullary (outside bone marrow) disease Particularly in CNS.

[3-5% had CNS disease at diagnosis] & If no CNS prophylaxis 50%-75% will develop CNS Disease]

Therefore all children with ALL should receive systemic combination chemotherapy some form of CNS prophylaxis In the form of :

1. **IT MTX, ARC, HD-MTX, HD-ARC, ± Cranial Irradiation**

With current CNS preventive therapy regimens, the incidence of CNS relapse is less than 10% overall & below 5% for good risk patients.

2. **Children with CNS disease at diagnosis should receive IT therapy plus CI or CSI.**

Status	CSF finding
CNS-1	No lymphoblasts
CNS-2	< 5 WBCs with blasts on cytospin
CNS-3	> 5 WBCs with blasts (or C.N. palsy)

Milestones in CNS Prophylaxis

1. ***SJCRH*-1970s- CSI (500-1200 cGy) –non preventive.**
2. **CI 2400 cGy plus 5 doses of IT MTX or CSI 2400 cGy alone, Reduced the incidence of CNS relapse to approximately 10%. `**

   BUT: **CSI : excessive myelosuppression & reduction of spinal growth**

Identification of LATE EFFECTS (brain abnormalities by CT scan altered intellectual and neuroendocrine dysfunction) after 2400 cGy ???—

***Another trial*---CI 1800 cGy plus 5 doses of IT MTX Appears to be as effective as 2400cGy BUT Still negative effect on neuro-cognitive function Greater adverse neuropsychological effect than IT MTX alone.**

***In a german trial*: CI 1200 cGy + intermediate dose MTX + re-induction was equally effective to 1800 cGy in STANDARD risk patients.**

Increased risk of CNS leukemia = preventive therapy? Patients:

- **High initial TLC** **Lymphadenopathy**
- **T-cell disease** **Hepatosplenomegaly**
- **Very young age** **Thrombocytopenia**

In late 90's an Italian group study (AIEOP) and the CCG – intensive CTh and IT MTx alone administered from the start of treatment throughout maintenance ttt. = 1800 cGy CI / so CI unnecessary for patients with a good prognosis

- **IT MTX alone given periodically throughout maintenance**

chemotherapy provide adequate CNS prophylaxis to these patients

For patients with intermediate risk and even high risk patients.

- **Only 10-15% of ALL patients (high risk) receive CI nowadays compared to 100% in the 60's & 70's.**
- **maintenance triple IT , the combination of IT + intermediate MTX**

& HD-MTX alone. All appear to provide equivalent protection to that offered by CI + IT. The intensity of Systemic chemotherapy appear to influence the efficacy of CNS preventive therapy regimens.

- **Trials evaluating efficacy and relative toxicity exploring safe removal of CI from CNS preventive ttt. Is underway.**

Isolated CNS Relapse: **<10% of patients.**

- **Intensive ttt. – EFS of 70%**
- **Depends largely on whether they received prior CNS irradiation**
- **Intensive chemotherapy & CSI secure long-term 2nd remission:**
  - **In 2/3 of previously un-irradiated patients.**
  - **1/3 in previously irradiated patient**

IT CTh for CNS remission induction (90% remission) followed by consolidation ttt. With CSI*(otherwise relapse within 3-4 mo) together with maintenance CTh.

- **CSI at a dose of 2,400 cGy is adequate but myelo-suppressive;**
- **CSF remission induction with IT CTh. Followed by CSI (cranial dose of 24-30 Gy & spinal dose of 12-18 Gy) is better.**

Determinants of success rate include:

1- Relapse > 18 mo (83% vs. 46%) EFS respectively

2- Initial CNS directed RT in their initial ttt.

Testicular relapse **(10-15% in 70's--- 2-5% recently)**

Diagnosis: US guided biopsy

24-30 Gy irradiations on both testes (even if one only is affected)

prognosis is better if isolated relapse.

LATE SEQULAE of RT

Neuro-Endocrine Dysfunction- impaired intellectual function
Obesity,
short stature,
Neuro-psychological deficits
Leuko-encephalopathy and microangiopathy.

ACUTE LEUKEMIA (adults)

PB and/or BM blasts ≥ 20 % of nucleated cell (NC) count

	Favorable	Unfavorable
Age	**15-20 yrs**	**>50 yrs**
WBC (B-lineage)	**<30,000/µL**	**>30,000/µL**
Time to CR	**CR in 2 - 4 ws**	**CR >4 ws**
MRD	**< 10^3 in consolidation & < 10^4 in maintenance**	**>10^3 in consolidation & > 10^4 in maintenance**
Immunophenotype	**Thymic T-ALL**	• **Pre B-ALL** • **Early T-ALL** • **Mature T-ALL**

Risk-adapted treatment of ALL

Cranial prophylaxis

1. **All standard-risk patients receive 18-24 Gy cranial irradiation (28 days after start of induction)**
2. **During cranial irradiation, MTX 15 mg intrathecal is given as 4 doses (twice / week)**

<u>The sanctuaries (CNS and testis)</u>

☞Treatment of CNS leukemia

A) Patients with initial CNS presentation

🕘 Are not regarded as high-risk based on this presentation alone.

If such patients receive adequate therapy, their prognosis is not worse.

- **However these patients should receive triple intrathecal therapy (and not MTX alone as usual)**

  - ***MTX 15 mg***
  - ***- ARA-c 40 mg***
  - ***- Dexa 4 mg***

<u>Further therapy</u>

Standard-risk pts

- **Cranio-spinal irradiation (24 Gy) after phase II of induction (in this situation, the irradiation is given as prophylaxis against recurrence. Patients are usually already free after ITH therapy) and ***<u>not after phase I</u>*** of induction as usual (higher toxicity).**
- **Triple intrathecal injections are given every 2 months for 2 years (irrespective whether maintenance treatment is indicated or not)**

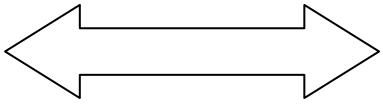
🡻High-risk pts

- **Patients will receive allo or auto BMT i.e: No CNS irradiation**

***🡻Patients with CNS relapse (± BM relapse*)**

such patients usually had cranial prophylaxis 24 Gy before

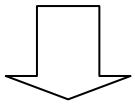
Complete 30 Gy on the cranium and add 24 Gy on the spine followed by triple ITH every 2 months for at least 24 months



<u>Treatment of special forms of AML-[High Risk Of CNS Disease]</u>

AML -M5(a-b) Monoblastic-monocytic- (30%) of cases

After reaching CR by induction chemotherapy, give triple intrathecal prophylaxis:Every 8 weeks for a total of 6 injections.



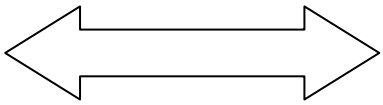
What to do if CNS disease was diagnosed at presentation ?

Give triple intrathecal injections until CSF is free then craniospinal irradiation is given (24 Gy).This is followed by double intrathecal injections in cases of CR with: ARA-c 40 mg

Dexamethazone 4 mg

Every 8 weeks for 7 doses Without MTX (to avoid leukoencephalopathy)

<u>N.B:</u> **If the patient is going to be transplanted, reduce craniospinal irradiation to 12 Gy to be given several days before conditioning by TBI/Cy.**



<u>Treatment Goals: for CLL</u>

> 55 years: Palliative intention-Better quality of life.-Control of symptoms.

? Increase survival.

< 55 years: Curative concept (purine analogue) 3 courses if no CR another 3 courses till CR --- HLA donor if < 45 years allogenic transplant ---if > 45 years mini-transplant

Treatment of CLL

Radiotherapy: Indications:

1. **Palliative in patients not responding to chemotherapy and in whom bulky disease is causing a local compression problem.**
2. **Patients with hypersplenism (has not been established) if splenectomy is contraindicated (low dose RT).**
3. **TBI remains investigational.**

CML –

1953-1963: palliative therapy→

1. **spleen irradiation (symptomatic) with daily doses of 25-50 cGy – gradual decrease in WBCs. With marked reduction after 5-10 Gy. While splenectomy is beneficial in case of hypersplenism.**
2. **Granulocytic sarcomas (chloromas) of soft tissues, brain, PNS, osseous deposits up to a dose of 30 Gy.**
3. **low dose TBI 10-25 cGy/F to a total dose of 150-200 cGy with 4-weeks gap after each 50-cGy to avoid TCP.**

Allogenic BMT – long term survival of 50-70%.

1.1 Consequences of CNS Prophylaxis in Children with Leukaemia

With current treatment protocols more than 50% of children with ALL may have a long-term survival or cure. A substantial proportion of the achieved results is attributed to the use of prophylactic measures aiming at controlling occult leukaemia cells in the CNS and meninges. At one time CNS prophylaxis used to include intrathecal methotrexate (ITMTX) cranial irradiation (CI) and intermittent high dose intravenously administered methotrexate (IV MTX). Each agent is associated with a small risk (1-2%) of white matter necrosis (leucoencephalopathy) The risk tends, however, to be more than additive (supra-additive) when CI is combined with MTX. A combination of CI (>20 Gy) and ITMTX (>50 mg) was shown to have a risk of 5% and this increased to 15% if CI was combined with IVMTX (40-80 mg/m^2/week). The worse combination is CI, IT MTX and IVMTX when the risk can be as high as 45%. Various explanations may be offered to account for the supra-additive effect:

1. Breakdown of the BBB induced by CI could be demonstrated in the rat. This can permit the penetration of normally excluded compounds (e.g. IV MTX) into the brain tissue.
2. Irradiation may alter the distribution kinetics of the drug so that some regions accumulate more drug than others.
3. Damage of the arachnoid granulations (villi) induced by radiation may delay reabsorption of CSF and the clearance of the drug from the CNS.
4. Irradiation may damage the specialised subependymal cells that normally constitute a barrier against diffusion of CSF so that IT MTX may diffuse across this barrier into the white matter.
5. MTX may act as a radiosensitiser.

Leucoencephalopathy may be clinically expressed as focal neurological manifestations of organic damage and disturbed neuropsychological functions with characteristic radiological changes as outlined below.

1.1.1.1 Neuropsychological functions after CNS prophylaxis

The neuropsychological functions of children with ALL (or other intracranial tumours such as medulloblastoma), can be tested by the application of a battery of psychomertic tests that cover testing for (a) intellectual abilities, (b) fine and gross motor abilities, (c) sensory perceptual abilities, (d) language skill, (e) memory and attention, and (f) school performance. The use of such a large battery improves the resolution of minor cognitive abnormalities. A lag of several months or even years exists before an impairment of cognitive functions is detected. It should be noted that the mean IQ of children with leukaemia may be greater than that of normal children. Young children before the age of six years are more susceptible to develop neuropsychological dysfunctions. A number of studies demonstrated that the cognitive consequences were more severe in patients whose CNS prophylaxis included cranial irradiation compared to children receiving ITMTX either alone or in combination with IVMTHX. The radiotherapy children had a lower mean full scale IQs, performed more poorly on tests measuring school abilities such as the Wide Range Achievement test (reading, spelling and arithmatics) and also scored low on a variety of other neuropsycological tests. The interpretation of these findings is subject to some discussion. Although irradiated children did significantly worse than the others, the performance of the irradiated children was still within the average score. It is also likely that that more of the high risk children were assigned to CI than to the other CNS prophylaxis measures. Moreover, it is known that the leukaemic process by itself may cause psychological and social problems that may render the interpretation of results difficult. At present the choice of a CNS prophylaxis procedure largely depends on the “risk status”. Low risk children are considered candidates for ITMTX alone. Standard risk children are chosen for intermediate

dose MTX plus ITMTX. Two options can be considered for high risk patients: CI + ITMTX versus high dose intensified systemic chemotherapy. The relative merits of the two regimens are currently investigated. In case that CI is chosen certain precautions should be considered
1.Give MTX before CI in order to avoid the radiation-induced vascular changes likely to alter the BBB and change the drug distribution pattern.
2. Reduce the total cranial irradiation dose to 18 Gy instead of 24 Gy.
3. Use a smaller dose per fraction
4. Use CSF markers to monitor the development of leucoencephalopathy. A significant increase in the concentration of albumin, lactate dehydrogenase (LDH), and myelin basic protein can serve as useful markers for early prediction of occurrence of encephalopathy.

1.1.1.2 Radiological findings after CNS prophylaxis

Abnormal CT and MRI brain-scan findings in children with ALL were first reported in symptomatic necrotising encephalopathy. However, abnormal findings could also be seen in asymptomatic patients who received CNS prophylaxis in the form of cranial irradiation (24 Gy) plus monthly ITMTX maintenance chemotherapy. In some reports the incidence of abnormalities amounted to 50% of asymptomatic patients. Abnormal CT brain scans may appear after a latency of several years. This diagnostic aid is therefore recommended during long-term follow-up. Three types of abnormalities have been described:
1. *Intracranial (IC) calcifications* after a latency of several years are most frequently seen in the basal ganglia. Most probably they represent mineralising microencephalopathy. Both CI and the cumulative systemic MTX doses are thought to contribute to the production of this lesion. IC calcifications are mostly observed in children who received prophylactic therapy while less than 8 years of age and this emphasises the greater sensitivity of the brain of young children.

2. *Ventricular and subarachnoid space dilatation* most probably represents cerebral cortical atrophy. Dilatation tends to remain stable for years.
3. Areas of decreased parenchymal attenuation (density) are reversible abnormalities.
The significance of these CT findings could be determined by correlating them with any associated psychological abnormalities. IC calcifications are often associated with impairment of cognitive functions. In contrast, the correlation between cortical atrophy and such functions is less evident.